REMARKS

I. Status of the Claims

Claims 9, 15, 17-18 have been amended, claims 13-14, 16, 32-33, and 36-37 have been canceled without prejudice or disclaimer. Claims 1-8, 10-12, 19-31, and 34-35 have been withdrawn as being directed to non-elected subject matter.

Claims 9 and 18 have been amended such that they are now independent claims that recite a "screening method for a prophylactic or therapeutic substance for diabetes or a renal disease." Support for the amendment can be found throughout the specification, for example, at page 31, lines 28-30, page 47, lines 9-14, and in Examples 1-4, which include page 73, lines 20-24, page 75, lines 3-10, and page 76, lines 5-11 and 13-17, and in Tables 2, 4, and 6. Claim 9 has been further amended to recite "cultivating a cell that contains an insulin gene or a gene under the control of an insulin promoter with a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:2 . . . in the presence and absence of a test substance, comparing the expression level of the insulin gene or the gene under the control of the insulin promoter in the presence and absence of the test substance, and selecting the test substance that changes the expression level of the insulin gene or the gene under the control of the insulin promoter as a candidate for the prophylactic or therapeutic substance." Support for the amendment can be found, for example, at page 32, lines 24-34 and continuing on page 33, lines 1-3, and page 38, lines 8-18. Claim 18 has been further amended to recite "comparing the expression level of the mRNA that encodes said protein or a partial peptide thereof in the presence and absence of the test substance, and selecting the test substance that changes the expression level of the mRNA as a candidate for the

prophylactic or therapeutic substance." Support for the amendment can be found, for example, at page 33, lines 17-34 and continuing on page 34, lines 1-2. Claim 15 has been amended to depend on claim 9 and to recite ". . . wherein the cell contains a polynucleotide comprising the nucleotide sequence shown by SEQ ID NO:1, which encodes the amino acid sequence shown by SEQ ID NO:2." Support for the amendment can be found, for example, at page 33, lines 27-31. Claim 17 has been amended to depend on claim 9 and to recite ". . . wherein the renal disease is diabetic nephropathy" Support for the amendment can be found, for example, at page 47, lines 9-14, and page 73, lines 20-24. Claims 38-43 have been added. Support for the new claims can be found, for example, at page 32, line 24 to page 33, line 3; page 33, lines 17-20; page 28, lines 29-31; page 47, line 29 to page 48, line 3 and 10-34; page 47, lines 9-14, and page 73, lines 20-24. Thus, the amendments are fully supported by the specification and no new matter has been added. Upon entry of these amendments, claims 9, 15, 17-18, and 38-43 are under consideration.

II. Objection to Title

The Office objected to the Title "because it does not accurately describe the claimed invention." As requested, Applicants have amended the title to: "Prophylactic or Therapeutic Substance for Diabetes or a Renal Disease Associated with TSC-22 and Screening Method Thereof."

III. Claim Rejections Under 35 U.S. C. 112, Second Paragraph

The Office has rejected claim 9 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for:

> failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, specifically, the claim depends from Claim 7, which recites "comparing the activities of proteins", and Claim 7 depends from Claim 1, which recites "using said protein", whereas Claim 9 recites a method of "comparing the expressions of said gene". Accordingly, it is unclear how the method of Claim 9 can depend from the methods of Claims 1 and 7, thus, the metes and bounds of the claim cannot be determined. Further regarding Claim 9, the method comprises only "a screening method", i.e., the method has no purpose. Accordingly, the method is considered to be vague and indefinite.

Office Action at page 2, paragraph 7. Applicants respectfully disagree.

Applicants have amended claim 9 such that it is now an independent claim and therefore, does not depend from claim 7 or 1. Claim 9 also now recites a "screening method for a prophylactic or therapeutic substance for diabetes or a renal disease" and that the screening method involves the steps of "cultivating a cell that contains an insulin gene or a gene under the control of an insulin promoter . . . in the presence and absence of a test substance, comparing the expression level of the insulin gene or the gene under the control of the insulin promoter in the presence and absence of the test substance, and selecting the test substance that changes the expression level of the insulin gene or the gene under the control of the insulin promoter as a candidate for the prophylactic or therapeutic substance." Thus, the claimed method does have a purpose. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Office has rejected claims 9 and 13-18 as being "incomplete for omitting essential steps, such omission amounting to a gap between the steps."[1] Office Action at page 2, paragraph 8. With respect to claims 9 and 18, the Office states:

> [T]he method comprises only the cultivating of a cell and the comparing of the expressions of a gene (Claim 9) or comparing amounts of mRNA (Claim 18). The claims fail to recite what the comparison will tell the skilled artisan, and in the case of Claim 18, how said comparison will result in a prophylactic or therapeutic substance.

Id. Applicants respectfully disagree.

Claim 9 now recites "comparing the expression level of the insulin gene or the gene under the control of an insulin promoter . . . in the presence and absence of a test substance, and selecting the test substance that changes the expression level of the insulin gene or the gene under the control of the insulin promoter as a candidate for the prophylactic or therapeutic substance." Claim 18 also now recites "comparing the expression level of the mRNA that encodes said protein or a partial peptide thereof in the presence and absence of the test substance, and selecting the test substance that changes the expression level of the mRNA as a candidate for the prophylactic or therapeutic substance." Thus, the claims clearly recite what the comparison will tell the skilled artisan, and how the comparison will result in a prophylactic or therapeutic substance. Accordingly, Applicants respectfully request withdrawal of the rejection.

[1] The Office Action at page 2 rejected claim "19" and 13-18 under 35 U.S.C. § 112, second paragraph, as allegedly being incomplete for omitting essential steps. Applicants believe the Office intended to reject claim "9" rather than claim "19," and have addressed the rejection accordingly.

The Office has rejected claims 13-17 because "the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass." Office Action at page 3, first paragraph. Applicants respectfully disagree.

Rejected claims 13, 14, and 16 have been canceled. Claim 15 now recites that the "cell contains a polynucleotide comprising the nucleotide sequence shown by SEQ ID NO:1, which encodes the amino acid sequence shown by SEQ ID NO:2" and depends from claim 9. Claim 17 also depends from claim 9. As noted above, claim 9 does recite steps involved in the method and therefore, Applicants assert that the claim is definite. Accordingly, Applicants respectfully request withdrawal of the rejection.

IV. Claim Rejection Under 35 U.S.C. 101

Claims 13-17 have been rejected under 35 U.S.C. § 101 because "the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101." Office Action at p. 3. Applicants respectfully disagree.

Claims 13, 14, and 16 have been canceled. As noted above, remaining claims 15 and 17 both depend from claim 9, which recites steps involved in the method. Therefore, withdrawal of the rejection is respectfully requested.

V. Claim Rejections Under 35 U.S. C. 112, First Paragraph

The Office has rejected claims 9 and 13-18 under 35 U.S.C. 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention." Office Action at page 3, paragraph 5. The Office alleges that:

> There is insufficient written description to show that Applicant was in possession of:
> A) "a disease associated with a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:2 or a salt thereof", except diabetes (Claims 1, 13, and 14), or
> B) "a gene whose expression is controlled by a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:2 or a partial peptide thereof or a salt thereof, except insulin (Claim 9).

Office Action at page 4, first paragraph.

With respect to (A) above, the Office states that "the specification discloses no diseases associated with a protein comprising the same or essentially the same amino acid sequence show by SEQ ID NO:2 or a salt thereof, except possibly diabetes." Office Action at page 4, paragraph 2. The Office alleges that the Applicants provide a list of unrelated diseases, and that "[a]bsent a common structure and function relating the diseases, which has not been established, one of skill in the art would conclude that the specification fails to adequately describe the claimed genus of diseases." *Id.*

Applicants respectfully traverse. The claims now recite "a prophylactic or therapeutic substance for diabetes or a renal disease." In contrast to the statement by the Office that the specification "discloses no diseases associated with a protein comprising the same or essentially the same amino acid sequence shown by SEQ ID NO:2 . . . except possibly diabetes," Applicants assert that the specification provides sufficient written description for diabetes and renal disease as being associated with a

protein comprising the same or substantially the same amino acid sequence as shown by SEQ ID NO:2 or a partial peptide thereof or a salt thereof. The specification shows an increase in the expression level of the rat TSC-22 mRNA, which encodes a protein that is 99% identical at the amino acid level to the human protein comprising SEQ ID NO:2, in the kidneys of three related rat models of human renal disease, including: 1) a "fatty" rat model of non-insulin-dependent diabetes that spontaneously develops diabetic nephropathy (*see* Example 1 and Table 2), 2) a rat model of hyperinsulinemia that develops renal disease (*see* Example 2 and Table 4), and 3) a rat model of hypercholesterolemia that develops renal disease (*see* Example 3 and Table 6).

Specifically, Example 1 discloses a Wistar fatty rat model, which develops non-insulin-dependent diabetes at 13 weeks of age, diabetic nephropathy at 22 weeks of age, and exhibits increased TSC-22 mRNA expression levels in kidney at 40 weeks of age. *See* specification at pages 73 and 74, lines 20-25 and 19-23, respectively, and Tables 1 and 2. Example 2 discloses a Zucker fatty rat model, which has hyperinsulinemia and spontaneously develops renal disease. *See* specification at page 75, lines 3-10. The Zucker fatty rats were treated daily with candesartan cilexitil or with a vehicle control, and TSC-22 mRNA expression levels were determined in kidney after nine weeks of treatment. *See* specification at pages 75 and 76, lines 3-10 and 5-11, respectively, and Table 4. The specification discloses that in the kidneys of the Zucker fatty rats with increased urinary albumin excretion, the "TSC-22 mRNA expression level increased and the mRNA expression of TGF-β1 also increased. Furthermore, when the increase in urinary albumin excretion was suppressed by administration of candesartan

cilexetil, both of the above-described increases in mRNA expression levels were suppressed." *See* specification at page 76, lines 5-11.

Furthermore, Example 3 discloses a rat model of hypercholesterolemia that spontaneously develops renal disease, and examined TSC-22 mRNA expression levels in kidney. *See* specification at page 76, lines 13-19. The specification discloses that "TSC-22 mRNA expression level increased 1.9 fold in the [spontaneous hypercholesterolemic] rats at 6 weeks of age, and thereafter the expression level increased over time. In the [spontaneous hypercholesterolemic] rats, the TSC-22 mRNA expression level showed a significant positive correlation with urinary albumin excretion . . . and with blood urea nitrogen concentration." *See* specification at page 77, lines 17-23. Example 4 used the spontaneous hypercholesterolemic rat model of Example 3 in *in situ* hybridization experiments to examine TSC-22 mRNA expression levels in kidney. *See* specification at page 78, lines 4-6. The specification discloses that "signals were observed in proximal tubules, thin-wall tubules, and epithelial cells of glomerular capsule and podocytes, and epithelial cells of distal tubules and collecting ducts, in SHC rat kidneys, with evidently greater signal intensity than in normal rats." *See* specification at p. 78, lines 25-29. The specification also states: "These results suggest a close association of the high expression of TSC-22 in the glomular and tubular epithelial cell systems and the onset of renal disease." *See* specification at page 79, lines 1-3. The specification also discloses that "[t]he disease associated with the protein of the present invention . . . is preferably a renal disease or diabetes, more preferably diabetic nephropathy." *See* page 31, lines 28-30. Thus, the specification sufficiently provides written description for diabetes and renal disease as being

associated with a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:2 or a partial peptide thereof or a salt thereof.

With respect to (B) above, the Office acknowledges that the specification discloses "the insulin gene and the like" as genes "whose expression is controlled by a protein comprising the same or substantially the same amino acid sequence shown by SEQ ID NO:2." Office Action at page 4, paragraph 3. The Office notes that "as genes comprising 'the like' are not disclosed, it appears that the specification discloses just a single species to represent the entire claimed genus of genes." *Id.* The Office suggests that an adequate written description would "require a disclosure of a common structure and function for the claimed genus of genes." *Id.* Applicants respectfully disagree.

Claim 9 recites the use of a cell "that contains an insulin gene or a gene under the control of an insulin promoter." The specification provides sufficient written description for an insulin gene or a gene under the control of an insulin promoter as genes whose expression is controlled by a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:2 or a partial peptide thereof or a salt thereof. For example, the specification states:

> As examples of the "gene whose expression is controlled by the protein or the like of the present invention," **the insulin gene** and the like can be mentioned. Alternatively, the gene may be chimeric DNA containing the cis-element of a promoter whose transcription activity is controlled by the protein or the like of the present invention (e.g., **insulin gene promoter** and the like), and... DNA that encodes various reporter proteins may be joined downstream of the promoter.

See specification at page 32, lines 24-31. Emphasis added.

Therefore, Applicants respectfully request withdrawal of the rejection.

VI. Claim Rejections Under 35 U.S. C. 103(a)

The Office has rejected claims 9 and 13-18 as allegedly being unpatentable over U.S. Patent No. 6,165,733 in view of Ihara et al. (2001). The Office states:

> The '733 patent teaches a screening method for a therapeutic substance (a mitogenesis inhibitor) comprising cultivating a cell (the contacted cell had to have been "cultivated") and comparing the expression of a gene in the presence or absence of a test compound (see particularly Claims 1 and 2). While the reference does not specifically teach the comparison of mRNA expression of Claim 18, comparisons of gene expression comprise either comparisons of DNA or mRNA expression such that either are readily envisioned as equivalents.

Office Action at page 5, paragraph 2.

The Office acknowledges that the '733 patent fails to "teach comparing the expression of a gene encoding the protein of SEQ ID NO:2." Office Action at page 5, paragraph 3. However, the Office also states:

> Ihara et al. teaches the protein of SEQ ID NO:2 (TSC-22), is associated with diabetes. In particular, the expression of the gene of SEQ ID NO:1 can be used as a marker for insulin expression. TSC-22 inhibits insulin expression such that a measure of TSC-22 expression can be used as a measure of insulin expression and the reduction of TSC-22 expression is an indication of increased insulin expression (see the entire Abstract) .

Office Action at page 5, paragraph 4.

The Office further suggests:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ

> the screening method of the '733 patent employing the measuring of the expression of the TSC-22 gene of Ihara et al. given the relationship of TSC-22 expression and insulin expression. Said method could be used as a method for screening test substances for their effect on TSC-22 expression as a measure of their efficacy as a therapeutic for the treatment of diabetes.

Office Action at page 5, paragraph 5.

Applicants respectfully traverse. As the Office acknowledged, nowhere does the '733 patent teach or suggest screening for a prophylactic or therapeutic substance for diabetes or a renal disease, which comprises cultivating a cell with a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:2 or a partial peptide thereof or a salt thereof (claim 9), or which comprises cultivating a cell having an ability to produce a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:2 or a partial peptide thereof or a salt thereof (claim 18). Thus, the Office combines Ihara et al., which allegedly teaches that the protein of SEQ ID NO:2 (TSC-22) is associated with diabetes. However, Ihara et al. fails to make up for the deficiencies of the '733 patent and, in fact, teaches away from the claimed invention.

Ihara et al. detected expression of TSC-22 in "the pancreatic islets of GK rat," which is a model of "non-obese type 2 diabetes mellitus." *See* Ihara et al., Abstract, lines 8 and 3-4, respectively. Ihara et al. "examined the effects of TSC-22 on the transcriptional activity of [the] insulin promoter" by generating a luciferase reporter downstream of the human insulin promoter, which was "transfected into [a] mouse derived insullinoma cell line... with or without [a] TSC-22 expression plasmid." *See* Ihara et al., Abstract, lines 11-15. Ihara et al. found that the "activity of [the] insulin

promoter was **repressed** to 58% of control by the expression of TSC-22." *See* Ihara et al., Abstract, lines 17-18 (emphasis added). Ihara et al. concluded that "TSC-22 may play a **suppressive role** in insulin gene expression in the pancreatic beta-cells of GK rats and also that it may be one of the candidate genes for type 2 diabetes mellitus." *See* Ihara et al., Abstract, lines 20-23 (emphasis added). Ihara et al. appears to teach the opposite of the instant invention. Example 1 of the instant specification shows "increased TSC-22 mRNA expression levels" in the Wistar fatty rats at 40 weeks of age, which was accompanied by an increase in plasma insulin concentrations. *See* page 74, Tables 1 and 2. This data suggests that an increase in TSC-22 is associated with an **increase** in insulin gene expression.

Moreover, Ihara et al. later cast doubt on their own work in Sugawara et al. ("Human TSC-22 Gene: No Association with Type 2 Diabetes," *Internal Medicine* 40:993-997, October 2001) (copy enclosed). In discussing what appears to be the work of the cited Ihara abstract, Sugawara et al. indicate that the recognition "that the human insulin gene promoter activity was repressed by the TSC-22 gene product" led them to speculate "that the quantitative or qualitative changes in the human TSC-22 gene may be involved in the pathogenesis of type 2 diabetes." Sugawara et al., p. 993, col. 2, first full paragraph. Thus, Sugawara et al. "examined whether or not a variation of the [TSC-22] gene is one of the factors involved in the development of type 2 diabetes." *Id.* at p. 993, col. 2, second full paragraph.

Sugawara et al. concluded that "[i]t is unlikely that the TSC-22 gene is a locus responsible for type 2 diabetes." *Id.* at Abstract. Sugawara et al. found two single nucleotide polymorphisms (SNPs) in the coding region of the first exon, two other SNPs

in the first intron, and one SNP in the putative promoter region of TSC-22. *Id.* However, there were "no significant differences in the frequency of these polymorphisms between patients with type 2 diabetes and non-diabetic control subjects." *Id.* Thus, Sugawara et al. undermined the earlier correlation between TSC-22 and the insulin gene that they suggested in Ihara et al.

Accordingly, it would not have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of the '733 patent with the teachings of Ihara et al. to arrive at the instant invention. Applicants respectfully request withdrawal of the rejection.

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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